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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,131	STAFFORD ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 17-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 17-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6-07, 9-07, 11-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-5, and newly added claims 17-45 are pending and under examination in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow.

2. This action is Non-FINAL as it contains new grounds of rejection based on the specification's definition of "increased sensitivity to warfarin".

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

4. The instant application claims priority to provisional application 60/505,527. The provisional application has been thoroughly reviewed. The effective filing date for each of the pending claims has been determined as follows:

Claims 1-5, 17, 19-22, 26-29, 33-36, and 40-43 do not find support in the '527 application and have been awarded the filing date of the instant application, that is 9/23/2004.

Claims 18, 23-25, 30-32, 37-39, and 44-45 find support in the '527 application and have been awarded benefit of the filing date of the '527 application, that is 9/23/2003.

Claim Rejections - 35 USC § 112

5. Claims 1, 3-5, 17, 21, 28, 35, and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) a method of identifying a Caucasian subject having an increased sensitivity to warfarin comprising: detecting in the vitamin K epoxide reductase (VKOR) gene of subject, the presence of a G to C alteration at position 2581 of SEQ ID NO: 11, wherein detection of a G to C alteration at position 2581 of SEQ ID NO: 11 is correlated with increased sensitivity to warfarin;

2) A method of screening for a single nucleotide polymorphism in the VKOR gene of a human subject which is associated with increased sensitivity to warfarin, comprising a) identifying a human subject with increased sensitivity to warfarin based on the subjects' maintenance dose of warfarin required to achieve a therapeutically effective response, b) detecting in a population of subjects of a) above the presence of a single nucleotide polymorphism in the VKOR gene, and c) correlating the presence of the single nucleotide polymorphism of step (b) with the increased sensitivity to warfarin in the population of subjects, thereby identifying a single nucleotide polymorphism in the VKOR gene correlated with increased sensitivity to warfarin;

3) A method of correlating a single nucleotide polymorphism in the VKOR gene of a human subject with increased sensitivity to warfarin, comprising: a) identifying a subject having increased sensitivity to warfarin based on the subjects' maintenance dose of warfarin required to achieve a therapeutically effective response; b) determining the nucleotide sequence of the VKOR gene in a population of the subjects of (a); c) comparing the nucleotide sequence of step (b) with the wild type nucleotide sequence of the VKOR gene; d) detecting a single nucleotide polymorphism in the nucleotide sequence of (b); and e) correlating the single nucleotide polymorphism of (d) with increased sensitivity to warfarin in the subject of (a); and

4) A method of screening for a single nucleotide polymorphism in the VKOR gene of a human subject that is associated with increased sensitivity to warfarin comprising: a) detecting single nucleotide polymorphisms in the VKOR gene of a human subject; b) performing a population based study to detect the polymorphisms in a group of human subjects identified as having increased sensitivity to warfarin based on the subjects' maintenance dose of warfarin required to achieve a therapeutically effective response, and ethnically matched controls; and c) identifying an allele of a single nucleotide polymorphism in the VKOR gene that is associated with increased sensitivity to warfarin.

does not reasonably provide enablement for the methods as recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and

whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

Claims 1 and 3 are broadly drawn to diagnostic methods of identifying a human subject having an increased sensitivity to warfarin by detecting in any human subject, of any ethnicity (such as Asian, Caucasian, African, African American, and Hispanic), the presence of any single nucleotide polymorphism in the VKOR gene, wherein the single nucleotide polymorphism is correlated with increased sensitivity to warfarin, thereby identifying the subject as having an increased sensitivity to warfarin.

Claims 4, 5, and 17 are directed to methods of identifying or correlating a single nucleotide polymorphism in the VKOR gene of a human subject with increased sensitivity to warfarin, where the claims include a step of identifying a human subject having increased sensitivity warfarin.

Claims 21, 28, 35, and 42 are specifically directed to methods of amplifying particular segments of the VKOR gene which "comprise an allele of a single nucleotide polymorphism that is correlated with increased sensitivity to warfarin".

The specification specifically defines a subject with "increased sensitivity to warfarin" as a subject for whom a suitable dose of warfarin is lower than the therapeutic or maintenance dose

suitable for a subject who did not carry a SNP in the VKOR gene that imparts a phenotype of increased sensitivity to warfarin (see page 15). The claims require a predictive association between any single nucleotide polymorphism in the VKOR gene (VKORC1) and warfarin sensitivity, in any human subject. Further, to practice the methods of 1, 3-5, and 17, as defined by the specification, one would have to have knowledge of particular alleles for each SNP in the VKOR gene which are associated with increased sensitivity to warfarin to be able to identify a subject as set forth in the claims.

The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The amount of direction or guidance and Presence and absence of working examples:

The specification teaches that a subject with "increased sensitivity to warfarin" is a subject for whom a suitable therapeutic or maintenance dose of warfarin is lower than the dose suitable for a "normal" subject, that is a subject who does not carry the SNP (page 15). The specification teaches that three mutations were identified in the VKOR gene: vk2581 G to C, vk3294 T to C, and vk4769 G to A, and were examined for a correlation between their presence in a subject and the maintenance dose of warfarin required to achieve a therapeutically effective response. The specification teaches that of the subjects studied, the average warfarin dose for patients (26) with the vk2581 G allele was 50.19 +/- 3.2 mg per week, while those heterozygous (17) and homozygous (15) for the C allele were 35.19 +/- 3.73 and 31.14 +/- 6.2 mg per week, respectively (page 21). The specification teaches identifying specific haplotypes in Caucasians

and that the distribution of individual SNPs in patients was found to be significantly correlated with others. The specification also teaches average warfarin doses for patients with the vk3294 and vk4769 polymorphisms (page 21, figures 1B and 1C).

The specification is silent with regard to analyzing whether such associations were found across different races or ethnicities of human subjects. Additionally, the claims broadly encompass the association between warfarin sensitivity by analyzing any single nucleotide polymorphism in the VKOR gene. Geisen (Geisen et al; Thromb Haemost. Vol 94, pages 773-779. 2005) teaches that there are over 25 SNPs in the VKOR gene (see table 1). However the specification is silent as to an association between these particular SNPs and warfarin sensitivity. The claims broadly encompass the investigation of a broad scope of possible genomic regions for alleles which are indicative of warfarin sensitivity. However, the specification provides no correlation between the identity of broadly any SNPs or any particular SNP, that is the structure, with the function or phenotype of warfarin sensitivity. Therefore, the skilled artisan would be unable to predictably correlate any structural change in any other region of VKORC1, and warfarin sensitivity.

The state of the prior art and the predictability or unpredictability of the art:

While the state of the art and level of skill in the art with regard to the detection of any known polymorphic allele is high, the level of unpredictability in associating any particular allele with a specific phenotype is even higher. There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in

genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker (Hacker et al; Gut, 1997, Vol. 40, pages 623-627) teaches that they were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population.

Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281; 1787-1789).

Additionally, Lucentini (The Scientist, page 20, December 20, 2004) reveals that most gene association studies are typically wrong. Lucentini teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph).

Similarly, Hegele (Arterioscler. Thromb. Vasc. Biol. vol 22; pages 1058-1061; 2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and

refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

With regard to VKOR polymorphisms, the identity of the nucleotide at position 2581 of SEQ ID NO 11, does not appear to be as predictably associated with warfarin sensitivity in any human population. For example, in table 2 of Reider (Reider et al; US Pregrant publication 2006/0084070), it can be seen that haplotype 3 contains a C at position 6853 (corresponds to position 2581 of SEQ ID NO: 11). However this haplotype is found in a number of African controls. Geisen teaches that warfarin sensitivity is known to vary between different ethnicities and that there is a significantly higher average warfarin requirement in subjects of African American ethnicity (page 778, coo. 1, 2nd full para). This teaching appears at opposite with the broad assertions set forth in the claims as the identity of the SNP at position 2581 would not appear to be predictive of warfarin sensitivity in this population. Additionally, as can be seen from the haplotypes in table 1 of Reider, a number of particular alleles of SNPs in VKOR are found in subjects who have warfarin sensitivity and warfarin resistance. Accordingly, it appears that not all SNPs would be predictive of warfarin sensitivity based on the finding that it was found in a single subject with warfarin sensitivity, particularly given the art acknowledged inter-individual and inter-ethnical variability in warfarin sensitivity (see Geisen and Reider).

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

Although the level of skill in the art is high, the unpredictability of associating polymorphisms with phenotypic traits is even higher. To practice the invention as broadly as it is claimed, the skilled artisan would have to perform a large study of cases and controls in different human populations to determine whether the C at position 2581 of SEQ ID NO: 11 was predictably associates with warfarin sensitivity in any population as well as characterize additional sequences within the VKORC1 gene and determine if they are predictably associated with warfarin sensitivity, as well as determining whether the polymorphisms are so associated in any population or whether the association is population specific. Given the unpredictability in the associated technology, this experimentation would be replete with trial and error experimentation, with the results of each analysis being unpredictable. Such experimentation is considered undue.

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

6. The response traverses the rejection.

The response asserts that the test for enablement is whether the experimentation is undue, and that a considerable amount of experimentation is permissible if it is merely routine. The response asserts that it is not whether any experimentation is necessary but rather whether one skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation (pages 5-6). The response asserts (page 7) that based on the teaching of claim 1, one of skill in the art would readily recognize that the method can be carried out in any human subjects of any race or ethnicity based on the knowledge which would be accessible to the ordinary artisan without undue experimentation and that it is not necessary that the specification teach each and every SNP and whether it is correlated with increased sensitivity to warfarin for one of ordinary skill to carry out the methods of the invention (page 8). The response asserts that SNPs are well known and readily identifiable and that determining warfarin dosages is well known, such that correlating SNPs with particular phenotypic traits is routine. The response reiterates these arguments at page 13. These arguments have been thoroughly reviewed but were not found persuasive. Although methods of detecting mutations or differences between nucleic acid sequences is routine, actually establishing an association between the mutations or polymorphisms is an unpredictable endeavor, as evidenced by the art cited. In this situation, the claims encompass a large number of possible nucleic acid mutations in the VKOR enzyme, however neither the specification, nor the art at the time of filing provided guidance to the skilled artisan to determine which polymorphisms or mutations are associated with warfarin sensitivity vs those that are not. The

claims encompass mutations or polymorphisms anywhere in the VKOR gene. The specification only teaches 3 polymorphisms in non coding sequences, however the specification does not teach how these mutations are associated with warfarin sensitivity. Although a mechanism or explanation is not an absolute requirement per se for enablement, in this situation the only guidance provided by the specification regarding a possible association with warfarin sensitivity is based on the genotype of 3 SNPs. However, the specification does not support the broad scope of the claims because the specification provides no guidance or rational as to which mutations or polymorphisms across the VKOR gene sequence are predictably associated with warfarin sensitivity vs not. The specification provides no guidance as to which of the essentially infinite possible choices is likely to be successful.

The response then cites 15 references (pages 8-9) as evidence that performing the methods of the invention were routine at the time of applicant's invention. The response asserts that once applicants identified the VKOR sequence and correlated SNPs with warfarin sensitivity, numerous other groups were able to find and report other SNPs associated with warfarin sensitivity and that the ordinary artisan has been proven to be fully capable of carrying out the methods of the invention without undue experimentation (page 11). The arguments and each of the references have been thoroughly reviewed but were not found persuasive to overcome the rejection. First, it is noted that all the references are dated after the filing date of the instant invention, and as such were not available to the skilled artisan at the time the invention was filed. Further, as noted above, although methods of detecting mutations or differences between nucleic acid sequences is routine, actually establishing an association between the mutations or polymorphisms is an unpredictable endeavor, as evidenced by the art

cited. In this situation, the claims encompass a large number of possible nucleic acid mutations in the VKOR enzyme, however neither the specification, nor the art at the time of filing provided guidance to the skilled artisan to determine which polymorphisms or mutations are associated with warfarin sensitivity vs those that are not. None of the additional SNPs identified by the post filing date art as being associated with warfarin response or dose requirement could be predicted based on the guidance in the instant specification. Of the at least 25 SNPs in the VKOR gene, only a subset of these have been found to be predictive of warfarin response and maintenance dose requirement, however the identity of the SNPs could not be predicted simply based on the guidance in the specification. As exemplified by the art cited, the skilled artisan would be required to perform unpredictable trial and error experimentation to determine which embodiments were operative vs those that were inoperative. Further, with regard to the arguments made at paragraph 2 of page 11, a number of the SNPs identified and correlated with warfarin response, after the instant invention was filed, do not appear to have been conceived by the instant specification, as the specification is silent as to their structure as well as to which are correlated with warfarin response vs those that are not.

The response further asserts (page 6) that the claims are quite specific in scope and not overly broad as they are directed to a defined phenotype of increased sensitivity to a specific drug and a defined genotype correlated with a defined phenotype. These arguments have been thoroughly reviewed but were not found persuasive. The claims rejected do not set forth any particular genotype, the phenotype of increased sensitivity to warfarin is defined based on genotype analysis, and the specification has provided no predictable correlation between any genotype and the phenotype of increased sensitivity to warfarin.

For these reasons and the reasons made of record above, the rejection is maintained.

Written Description

7. Claims 1, 3-5, 17, 21, 28, 35, and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 3 are broadly drawn to diagnostic methods of identifying a human subject having an increased sensitivity to warfarin by detecting in any human subject, of any ethnicity (such as Asian, Caucasian, African, African American, and Hispanic), the presence of any single nucleotide polymorphism in the VKOR gene, wherein the single nucleotide polymorphism is correlated with increased sensitivity to warfarin, thereby identifying the subject as having an increased sensitivity to warfarin.

Claims 4, 5, and 17 are directed to methods of identifying or correlating a single nucleotide polymorphism in the VKOR gene of a human subject with increased sensitivity to warfarin, where the claims include a step of identifying a human subject having increased sensitivity warfarin.

Claims 21, 28, 35, and 42 are specifically directed to methods of amplifying particular segments of the VKOR gene which "comprise an allele of a single nucleotide polymorphism that is correlated with increased sensitivity to warfarin".

The specification specifically defines a subject with "increased sensitivity to warfarin" as a subject for whom a suitable dose of warfarin is lower than the therapeutic or maintenance dose suitable for a subject who did not carry a SNP in the VKOR gene that imparts a phenotype of increased sensitivity to warfarin (see page 15).

The claims therefore encompass methods of using a large genus of single nucleotide variants, including deletions, substitutions, and insertions at any site within the VKOR (VKORC1) gene. This genus includes a large number of polymorphisms and mutations for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named 3 polymorphisms for which data is provided. This data, however, does not provide for a predictable association between any single nucleotide polymorphism in the VKOR gene and warfarin sensitivity, as is broadly claimed. Here, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms with the recited phenotype. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with warfarin sensitivity is provided. Further, although the specification teaches that the SNPs in intron 2 and the 3' UTR are linked, as evidenced by the teachings of Reider (US Pregrant Publication 2006/0084070), the polymorphisms in intron 2 and the 3' UTR are not necessarily predictably indicative of each other (see Tables 1 and 2, the last three SNPS taught by Reider correspond to the SNPs at position 2581, 3294, and 4769 of instant SEQ ID NO: 11), where the haplotypes CTG, CCG, GTG, GCG, and GCA are found.

The claims broadly encompass the investigation of a broad scope of possible genomic regions for alleles which are indicative of warfarin sensitivity. However, the specification provides no correlation between the identity of broadly any SNPs, that is their structure, with the function or phenotype of warfarin sensitivity. Therefore, the skilled artisan would be unable to predictably correlate any structural change in any region of the VKOR gene, and warfarin sensitivity.

The individual polymorphisms set forth in the specification are not representative of the genus of any polymorphism associated with warfarin sensitivity, because it is not clear which polymorphisms within the broad region encompassed by the claims would have the same affect.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and polymorphisms, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Response to Arguments

8. The response traverses the rejection. Arguments made with regard to claim 1 being an original claim will not be addressed as the office action did not set forth that claim 1 was directed to new matter. The arguments that claim 1 is a method claim and not a product claim (page 15, para 2 of the response) has been thoroughly reviewed but was not found persuasive to overcome the rejection. The claim is drawn to a method of using a large genus of nucleotide variants, for which no adequate written description is provided in the specification for the reasons set forth above. The response cites example 18 "Process claim where the novelty is in the method steps" of the Revised Interim Written Description Training Materials. It is noted that the Training Materials were revised in March 2008. Accordingly, in response to this argument, the examiner will use the analagous example, example 16, directed to "Process Claim where novelty resides in the method steps". The response asserts that with regard to the instant invention, and the method of claim 1, the specification reveals that the detection in a human subject of a SNP correlated with increased sensitivity to warfarin is essential to the function/operation of the claimed invention and that a particular SNP is not essential. This argument has been thoroughly reviewed but was not found persuasive because the method of claim 1 could not be practiced without knowledge of which particular SNPs are associated with increased sensitivity to warfarin vs not. Of particular note is the following statement made in the Training materials with regard to example 16 "The *degree of predictability within the claimed genus is high* because introduction of nucleic acid into mitochondria is disclosed to depend on complexing with compound X... According to the specification, those conditions would be expected to result in transformation regardless of which nucleic acid is complexed...". This is in contrast to the

instant claims where the *degree of unpredictability within the claimed genus is extremely high*. The method could not be practiced with any VKOR SNP or mutation, but rather requires a SNP which is functionally associated with warfarin sensitivity. The *Eli Lilly* court held that a fully described genus is one for which a person skilled in the art can "visualize or recognize the identity of the members of the genus". In the instant case, the prior art, the specification, and the postfiling date art do NOT support an association between every VKOR SNP or mutation and warfarin sensitivity/resistance. Further the specification does not describe which of each of the VKOR SNPs belong to the claimed genus vs not. In this instance, the genus is defined within the claim entirely by function. In contrast, the instant specification does not provide guidance regarding what structural features are responsible for the claimed function. Accordingly, the specification does not provide sufficient guidance to the skilled artisan to distinguish members of the claimed genus from non members (mutations or SNPs not associated with warfarin sensitivity/resistance). For these reasons and the reasons already made of record above, the rejection is maintained.

New Matter

9. Claims 17, 19, 22, 26, 29, 33-36, and 40-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter Rejection.

The following subject matter in the newly added claims, does not appear to be supported by the disclosure:

New claim 17 recites “ethnically matched controls”. The response asserts that support is found at page 16, line 14 to page 17 line 14; and on pages 19-22. The specification has been thoroughly reviewed but does not provide support for ethnically matched controls. It is noted that at page 20 of the response, applicants assert that the Examiner applicant’s disclosure and the available art render the method of claim 17 enabled and therefore patentable. However, enablement and written description are severable requirements of 35 USC 112, first paragraph.

Newly added claims 19, 26, 33 and 40 recite "an amplified segment" which is "less than 100 base pairs in length". While the specification provides support for specific lengths of fragments, such as primers which are at least 15 nucleotides in length, the specification provides no support for an oligonucleotide that is "less than 100 base pairs in length", either synthetically produced or as a product of amplification.

Newly added claims 34, 35, 41 and 42 are directed to amplifying segments of the VKOR1 coding sequence and more specifically to segments which contain a SNP (claims 34 and 41) which are correlated with increased sensitivity to warfarin. Accordingly, the claims are directed to SNPs as well as SNPs which are correlated with increased sensitivity to warfarin, in the VKOR1 coding region, which is not supported by the specification.

Newly added claims 22, 29, 36, and 43 recite "wherein the nucleic acid sample is from a subject in need of warfarin therapy". The specification has been thoroughly reviewed, however this recitation was not found. At Example 1, page 20, the specification provides primers which were used to amplify VKOR nucleic acids from subjects receiving warfarin therapy, however it is not clear from the disclosure whether the primers are contained within SEQ ID NO: 8 or 9. Additionally, a subject in need of warfarin therapy is not necessarily a subject receiving warfarin,

however the specification at pages 19-22 does not appear to provide support for the amplification steps in a subject in need of warfarin therapy but not receiving warfarin.

Accordingly, the newly added claims appear to have introduced new matter into the claimed invention.

Claim Interpretation

10. Claim interpretation relevant to rejections under 35 USC 102 and 103 below:

11. The terms "5' end" and "3'end" have been given their broadest reasonable interpretation. They are not limited to sequences which must include the 5' or 3' terminal nucleotide of the recited SEQ ID NOS given. For example, a nucleic acid molecule may have many nucleotides encompassed by the term "5' end" as long as there is a nucleotide 3' to it. Likewise, a nucleic acid molecule may have many nucleotides encompassed by the term "3' end" as long as there is a nucleotide 5' to it.

12. Although the specification specifically defines the term "increased sensitivity to warfarin" based on genotype analysis, for the purpose of applying art under 35 USC 102 or 103, the recitation when included as a specific step in claims 3 (step a), 4 (step a), 5 (step a), and 17 (step b), has been given it's broadest reasonable interpretation. Methods of determining the warfarin maintenance dose required to achieve INR were known in the art at the time the invention was made. For example Aithal (Aithal et al; The Lancet, vol 353, 1999; pages 717-719) teaches that there exists widespread inter-individual variation in the response to a given dose of warfarin with an effective daily dose ranging from 0.5 mg to 60 mg. Individuals who are sensitive to warfarin require lower doses than individual who are more resistant.

13. The term VKOR is defined by the specification to designate vitamin K epoxide reductase (see page 2 line 5). Accordingly, the term VKOR is interpreted to be directed to the vitamin K epoxide reductase gene, rather than a multiprotein complex. The use of other acronyms in the art to refer to vitamin K epoxide reductase include VKORC1.

Claim Rejections - 35 USC § 102

14. Claims 1, 3, 20-22, 27-29, 34-36 and 41-43 are rejected under 35 U.S.C. 102(e) as being anticipated by Oldenburg (Oldenburg et al; US Pregrant publication 2005/0271644.

With regard to claims 1 and 3, Oldenburg teaches a method of determining polymorphisms in the VKOR (VKORC1) gene (see para 0168, 0170, 0171 and example 8), associated with warfarin sensitivity/resistance. With regard to claims 1 and 3, it is noted that although Oldenburg teaches specific mutations in subjects with warfarin resistance (C to T at position 292, for example), the term "increased sensitivity to warfarin" is a relative term and depends on the comparison. The specification defines a subject with "increased sensitivity to warfarin" as a subject for whom a suitable dose of warfarin is lower than the therapeutic or maintenance dose suitable for a subject who did not carry a SNP in the VKOR gene that imparts a phenotype of increased sensitivity to warfarin (see page 15). In the instant situation, Oldenburg teaches subjects with specific mutations with increased resistance to warfarin, therefore needing higher doses of warfarin, and thus do not carry a SNP which imparts increased sensitivity to warfarin. By comparison, Oldenburg further teaches that 384 controls do not carry the mutations which are associated with higher warfarin doses. These controls (C at position 292) would require lower warfarin doses than the subjects (T at position 292) identified by

Oldenburg who do not carry a SNP which imparts an increased sensitivity to warfarin and thus meet the limitation of the claims.

With regard to claims 20-22, 27-29, 34-36 and 41-43 Oldenburg teaches that genomic DNA of the human patient is isolated and the coding sequence is amplified by PCR using primers (para 0170, 0212-0214, and 0228-0238). Oldenburg teaches detecting polymorphisms as noted above. Oldenburg teaches PCR amplification in subjects in need of warfarin therapy (see para 0212-0214).

15. Claims 1, 3, 20-22, 27-29, 34-36 and 41-43 are rejected under 35 U.S.C. 102(a) as being anticipated by Rost (Rost et al; Nature vol. 427, pages 537-541 February 5, 2004).

With regard to claims 1 and 3, Rost teaches a method of determining polymorphisms in the VKOR (VKORC1) gene (see abstract, page 537, col 2), associated with warfarin sensitivity. With regard to claims 1 and 3, it is noted that although Oldenburg teaches specific mutations in subjects with warfarin resistance (C to T at position 292, for example), the term "increased sensitivity to warfarin" is a relative term and depends on the comparison. The specification defines a subject with "increased sensitivity to warfarin" as a subject for whom a suitable dose of warfarin is lower than the therapeutic or maintenance dose suitable for a subject who did not carry a SNP in the VKOR gene that imparts a phenotype of increased sensitivity to warfarin (see page 15). In the instant situation, Rost teaches subjects with specific mutations with increased resistance to warfarin, therefore needing higher doses of warfarin, and thus do not carry a SNP which imparts increased sensitivity to warfarin. By comparison, Rost further teaches that 384 controls do not carry the mutations which are associated with higher warfarin doses. These

controls (C at position 292) require lower warfarin doses than the subjects (T at position 292) identified by Rost who do not carry a SNP which imparts an increased sensitivity to warfarin and thus meet the limitation of the claims. Further, as evidence that the terms regarding increased "sensitivity" and "resistance" to warfarin is based on comparison, Rost teaches that "sensitive" rats were homozygous for tyrosine at position 139 whereas 12 and 4 "resistant" rats were homozygous and heterozygous, respectively for the Tyr139Cys mutation.

With regard to claims 20-22, 27-29, 34-36 and 41-43 Rost teaches that genomic DNA of the human patient was isolated and the coding sequence amplified by PCR using primers (page 537, para bridging cols 1 and 2, page 540 "Sequence Analysis). Rost teaches detecting polymorphisms as noted above. Rost teaches PCR amplification in subjects in need of warfarin therapy.

Response to Arguments

16. The response traverses the rejections under 35 USC 102(a) and (e) and asserts that the claims, as amended, define "increased sensitivity to warfarin". This argument has been thoroughly reviewed but was not found persuasive for the reasons made of record above.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 3-5 are rejected under 35 U.S.C 103(a) as being unpatentable over Oldenburg in view of Aithal (Aithal et al; The Lancet, vol 353, pages 717-719; 1999).

Oldenburg teaches a method of determining polymorphisms in the VKOR (VKORC1) gene (see para 0168, 0170, 0171 and example 8). Oldenburg teaches identifying warfarin resistant subjects based on their abnormal response to oral warfarin administration, identifying in a population of the subjects the presence of a mutation/polymorphism in the VKOR gene (claim 4b and 5b-d) and correlating the presence of the polymorphism/mutation in the VKOR gene with warfarin response (claim 3, 4c, 5e) (see para 0212-0214). Oldenburg does not specifically teach identifying subjects with increased warfarin sensitivity based on their response to oral warfarin administration, however Aithal teaches identifying patients with warfarin dose requirement of 1.5 mg or less, detecting polymorphisms in the CYP2C9 gene and correlating the genotype with warfarin sensitivity (see page 717, col 2 to page 718 col 1 "Methods"). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to screen the VKOR gene in human subjects for additional SNPs associated with different warfarin

dose requirements as taught by Oldenburg, including human subjects who require lower warfarin dose due to impaired metabolism as taught by Aithal. The ordinary artisan would have been motivated to screen for additional SNPs in the VKOR gene associated with warfarin dose requirements as Oldenburg teaches that vitamin K epoxide reductase is a component of the vitamin K cycle (VKOR complex) which is targeted by coumarins (warfarin) (see para 0002-0006, 0011).

20. Claims 3-5 are rejected under 35 U.S.C 103(a) as being unpatentable over Rost in view of Aithal (Aithal et al; The Lancet, vol 353, pages 717-719; 1999).

Rost teaches a method of determining polymorphisms in the VKOR (VKORC1) gene (see page 537, col 2). Rost teaches identifying warfarin resistant subjects based on their response to oral warfarin administration (see page 540, col. 1 "Subjects"), identifying in a population of the subjects the presence of a mutation/polymorphism in the VKOR gene (claim 4b and 5b-d) and correlating the presence of the polymorphism/mutation in the VKOR gene with warfarin response (claim 3, 4c, 5e) (see para page 537, col. 2). Rost does not specifically teach identifying subjects with increased warfarin sensitivity based on their response to oral warfarin administration, however Aithal teaches identifying patients with warfarin dose requirement of 1.5 mg or less, detecting polymorphisms in the CYP2C9 gene and correlating the genotype with warfarin sensitivity (see page 717, col 2 to page 718 col 1 "Methods"). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to screen the VKOR gene in human subjects for additional SNPs associated with different warfarin dose requirements as taught by Rost, including human subjects who require lower warfarin dose

(and are therefore sensitive to warfarin) due to impaired metabolism as taught by Aithal. The ordinary artisan would have been motivated to screen for additional SNPs in the VKOR gene associated with warfarin sensitivity/resistance as Rost teaches that vitamin K epoxide reductase is a component of the vitamin K cycle (VKOR complex) which is targeted by coumarins (warfarin) (see abstract, page 538 and 539). Further, Rost teaches that in warfarin resistant vs sensitive wild caught rats, the sensitive rats were homozygous for tyrosine at position 139 whereas 12 and 4 resistant rats were homozygous and heterozygous, respectively for the Tyr139Cys mutation, providing a link between mutations in vitamin k epoxide reductase and sensitivity and resistance to warfarin.

21. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rost or Oldenburg, each in view of Aithal, as applied to claims 3-5 above, and further in view of Risch (Nature, vol. 405, pages 847-856; 2000).

The teachings of Rost in view of Aithal, and the teachings of Oldenburg in view of Aithal are set forth above. Rost & Aithal, and Oldenburg & Aithal do not teach methods of performing studies in a population of subjects with increased sensitivity to warfarin based on warfarin dose requirements and ethnically matched controls. However, Risch teaches that optimal study design for screening for correlations between a genotype and phenotype should include the use of ethnically matched cases and controls (see page 854, col. 1). Risch teaches that if cases and controls are not ethnically comparable, then differences in allele frequency will emerge at all loci that differentiate these groups whether the alleles are causally related or not. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was

made improve the method of Rost & Aithal, or Oldenburg & Aithal to include studies with ethnically matched controls as taught by Risch. The ordinary artisan would have been motivated to include the use of ethnically matched controls to avoid stratification.

22. Claims 18-21 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over ss1516544 (dbSNP rs7294, build 86: 10/16/2000) or in the alternative ss12359507 (dbSNP rs8050894; build 116: 8/7/2003) each in view of Oefner (US Patent 6,453,244).

With regard to claims 20-21 and 27-28:

ss1516544 teaches a G/A SNP in a VKOR genomic sequence which corresponds to position 4769 of SEQ ID NO: 11). ss1516544 does not teach how to detect the SNP.

ss12359507 teaches a C/G SNP in a VKOR genomic sequence which corresponds to position 2581 of SEQ ID NO: 11). ss12359507 does not teach how to detect the SNP.

With regard to claims 18 and 25, Oefner teaches a method of detecting polymorphisms by denaturing high performance liquid chromatography which involves PCR amplifying a genetic region using primers that flank a polymorphic site to produce a short amplicon that can be tested for the presence of a polymorphism (see col. 13, lines 4-10). With regard to claims 19 and 26, Oefner teaches that the nucleic acid oligomers to be analyzed are preferably from 40-90 nucleotides long (see col. 13, lines 47-50; col. 20, lines 41-45).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the method of Oefner to detect mutations/polymorphisms in the genomic nucleic acid sequences taught by ss1516544 or ss12359507. The ordinary artisan would be motivated to use the method of Oefner to detect mutations/polymorphisms in the

genomic nucleic acid sequences taught by ss1516544 or ss12359507 because Oefner teaches it is an effective method to detect allelic variants in nucleic acid sequences.

23. Claims 18-21, 25-28, 32-35 and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyman (WO 99/33983) in view of Oefner (US Patent 6,453,244).

Lyman teaches a nucleic acid molecule designated SEQ ID NO: 1 which is 492 nucleotides long and is identical to positions 48 to 539 of instant SEQ ID NO: 9 (SEQ ID NO: 8 is a genomic fragment which contains the coding sequence of SEQ ID NO: 9, accordingly, a primer that is chosen from SEQ ID NO: 9 would also be from SEQ ID NO: 8). With regard to claims 20-21, 27-28, 34-35 and 41-42, Lyman teaches that nucleic acids include allelic variants of SEQ ID NO: 1 (page 4, lines 10-11). With regard to claims 18, 25, 32 and 39, Lyman does not teach how to detect the allelic variants, however Oefner teaches a method of detecting polymorphisms by denaturing high performance liquid chromatography which involves PCR amplifying a genetic region using primers that flank a polymorphic site to produce a short amplicon that can be tested for the presence of a polymorphism (see col. 13, lines 4-10). With regard to claims 19, 26, 33 and 40, Oefner teaches that the nucleic acid oligomers to be analyzed are preferably from 40-90 nucleotides long (see col. 13, lines 47-50; col. 20, lines 41-45).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the method of Oefner to detect mutations/polymorphisms in the nucleic acid sequence taught by Lyman. The ordinary artisan would be motivated to use the method of Oefner to detect mutations/polymorphisms in the nucleic acid sequences taught by

Lyman because Oefner teaches it is an effective method to detect allelic variants in nucleic acid sequences.

24. Claims 23-24 and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over ss1516544 (dbSNP rs7294, build 86: 10/16/2000) or in the alternative ss12359507 (dbSNP rs8050894; build 116: 8/7/2003) each in view of Oefner (US Patent 6,453,244) as applied to claims 18-21 and 25-28 above, and further in view of Keller and Manak (Keller and Manak. DNA Probes 2nd Ed; Macmillan Publishers Ltd.; 1993; page 259).

The teachings of ss1516544 or ss12359507 each in view of Oefner are set forth above. ss1516544 or ss12359507 each in view of Oefner do not teach primer lengths, however Keller and Manak teach that PCR primers are typically 15-30 nucleotides long. Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize primers that are at least 15 nucleotides long in the method of ss1516544 or ss12359507 each in view of Oefner because Keller and Manak teach that PCR primers are typically 15-30 nucleotides long.

25. Claims 23-24, 30-31, 37-38 and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyman (WO 99/33983) in view of Oefner (US Patent 6,453,244) as applied to claims 18-21, 25-28, 32-35 and 39-42 above, and further in view of Keller and Manak.

The teachings of Lyman (WO 99/33983) in view of Oefner are set forth above. Lyman in view of Oefner do not teach primers which are at least 15 nucleotides long, however Keller and Manak teach that PCR primers are typically 15-30 nucleotides long. Therefore it would

have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize primers that are at least 15 nucleotides long in the method of Lyman in view of Oefner because Keller and Manak teach that PCR primers are typically 15-30 nucleotides long.

26. Claims 19, 26, 33, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oldenburg or Rost, each in view of Oefner.

The teachings of Oldenburg are set forth above in section 14. The teachings of Rost are set forth above in section 15. Oldenburg or Rost do not teach producing an amplicon that is 100 base pairs or less. However Oefner teaches a method of detecting polymorphisms by denaturing high performance liquid chromatography which involves PCR amplifying a genetic region using primers that flank a polymorphic site to produce a short amplicon that can be tested for the presence of a polymorphism (see col. 13, lines 4-10). Oefner teaches that the nucleic acid oligomers to be analyzed are preferably from 40-90 nucleotides long (see col. 13, lines 47-50; col. 20, lines 41-45).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the method of Oefner to detect mutations/polymorphisms in the method of Oldenburg or Rost. The ordinary artisan would be motivated to use the method of Oefner to detect mutations/polymorphisms in method of Oldenburg or Rost because Oefner teaches it is an effective method to detect allelic variants in nucleic acid sequences.

Conclusion

27. No claims are allowed.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday, Wednesday and Thursday from 9:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Art Unit 1634